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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/375,333	08/16/1999	HERMANN OPPERMANN	STK-075	4896

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/375,333	Applicant(s) OPPERMANN ET AL.	
	Examiner David S Romeo	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *6-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-19* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6, 11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Ex parte prosecution is resumed. Claims 1-19 are pending.

In an interview with Karen Mangasarian on January 9, 2003 the examiner offered to revise the restriction requirement mailed July 2, 2001 (Paper No. 7) such that groups I-VIII, claims 1-5, were a single group and the examiner requested an election of a single species of TGF-β family member and a single species of heterologous leader sequence. In response, Attorney Mangasarian elected claims 1-5, formerly groups I-VIII, the species OP-1, and the species tissue targeting domain that binds a cell surface molecule on the surface of an osteoprogenitor.

Applicant's election with traverse of group I, claims 1-5, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that an examination of groups I-XXXVI does not impose a serious search burden, a search of a truncated leader sequence would be co-extensive with a search of a heterologous leader sequence, groups XII-XXXVI directed to heterodimers should not be separated from groups I-VIII because the searches are coextensive, and the groups are classified the same. This is found persuasive in part and groups I-VIII have been joined, as indicated above. With respect to remaining groups this is not found persuasive because the elected invention, truncated sequences and heterodimers are distinct both physically and functionally, and are not required one for the other. The elected invention does not require a truncated sequence, or a heterodimer. Nor does the truncated sequence require a heterodimer. Therefore, a search and examination of all the groups in one application would result in an undue

burden since the searches would not be co-extensive. Group XXXVI is not classified in the same class and subclass. Separate classification is not required to show a serious burden on the examiner if the inventions are distinct both physically and functionally, and are not required one for the other.

The requirement is still deemed proper and is therefore made FINAL.

Claim 6-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

The disclosure is objected to because of the following informalities: There are blank spaces at pages 1, 76, 80, where U.S. patent application serial numbers are supposed to be.

Appropriate correction is required.

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See page 95. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply

with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite over the recitation of "competent to refold under suitable refolding conditions" because the phrase "biologically active TGF-beta family member" presumes a correctly folded protein in its native state or folding pattern and it is unclear what further folding is intended or encompassed by "competent to refold under suitable refolding conditions". The metes and bounds are not clearly set forth.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Hall (WO 96/39430, cited by Applicants) in view of Suzuki (u12), Curiel (a12), and Hruska (b12). Hall teaches a transforming growth factor-β fusion protein, a method of preparation of the transforming growth factor-β fusion protein and methods of using the transforming growth factor-β fusion protein. The transforming growth factor-β fusion protein comprises a purification tag, at least one proteinase site, an extracellular matrix binding site, and a transforming growth factor active fragment. The method of preparation transforming growth factor-β fusion protein comprises purifying and renaturing transforming growth factor-β protein to provide an active transforming growth factor-β fusion protein preparation. See page 2, line 27, through page 28, line 3. As used therein, transforming growth factor-β fusion protein means the active portion of TGF-β, TGF-β1, TGF-β2 and TGF-β3 (page 3, lines 20-23). In one embodiment extracellular matrix (ECM) binding domains are used which are selective for either

collagen, fibronectin, or cell surface (page 4, line 28, through page 5, line 5). The ECM binding domain may be SEQ ID NO: 16 (page 51, claim 10). Illustrative combinations of fusions proteins suitable for use are summarized in Table I. See also page 5, lines 6-21. The recombinant TGF-β1-F2 fusion protein bound type I collagen (Example 10, pages 21-22). Suzuki teaches that bone is composed of type I collagen (paragraph bridging pages 1799-1800). Accordingly, Hall teaches a biologically active TGF-β family member fusion protein comprising a tissue targeting domain that binds to a bone matrix protein. Hall's SEQ ID NO: 16 is the RGD motif. Peptides containing the RGD motif bind $\alpha_v\beta_3$ integrin very efficiently. See Curiel, column 16, paragraph 0147. Hruska discloses localization of the $\alpha_v\beta_3$ integrin in human osteoprogenitor cells (Figure 1, column 3, lines 26-27). Accordingly, Hall's TGF-β fusion protein comprising an ECM binding domain, wherein the domain is SEQ ID NO: 16, comprises a tissue targeting domain that binds to a cell surface molecule on an osteoprogenitor.

Claims 1-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Nimni (c12) in view of Curiel (a12) and Hruska (b12). Nimni discloses a BMP-7 fusion protein comprising an extracellular matrix (ECM) binding site, wherein the ECM binding site is SEQ ID NO: 16, SEQ ID NO: 18, or SEQ ID NO: 20 (column 3, lines 37-55). The binding site facilitates delivery of the fusion protein to the desired site of action. The binding site is, therefore, chosen to direct the TGF-β/BMP to the site to be healed or where bone growth is required. Delivery of the TGF-β/BMP to the site to be treated reduces the amount of TGF-β/BMP required to be administered to be effective and reduces the concentration of circulating TGF-β/BMP which may result in undesirable side effects. Additionally, the binding of the TGF-β/BMP to the desired target site

prevents or inhibits diffusion of the TGF-β/BMP from the target site thus increasing the dose of the TGF-β/BMP at the target site. See paragraph bridging columns 3-4. Binding domains are used which are selective for either collagen, fibronectin or cell surface. In the case of BMP, binding sites present in bone are used. In this case it may be desirable to use the purification tag $(His)_6$ as the binding domain since $(His)_6$ bind to the hydroxyapatites of bone. See column 4, lines 23-65. Nimni's SEQ ID NO: 16 is the RGD motif. Peptides containing the RGD motif bind $\alpha_v\beta_3$ integrin very efficiently. See Curiel, column 16, paragraph 0147. Hruska discloses localization of the $\alpha_v\beta_3$ integrin in human osteoprogenitor cells (Figure 1, column 3, lines 26-27). Accordingly, Nimni's BMP-7 fusion protein comprising an ECM binding domain, wherein the domain is SEQ ID NO: 16, comprises a tissue targeting domain that binds to a cell surface molecule on an osteoprogenitor.

Claim Rejections - 35 USC § 112

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to or encompass various targeting domains. Each targeting domain is a genus of molecules defined only by function. The specification and claim do not indicate what distinguishing structural attributes are shared by the members of the genus. The specification and claim do not place any limit on the structure of the targeting domain. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is

permitted. The specification and claim do not provide any guidance as to requisite structure. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a targeting domain defined solely by function alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Recent Statutory Changes to 35 U.S.C. § 102(e)

On November 2, 2002, President Bush signed the 21st Century Department of Justice Appropriations Authorization Act (H.R. 2215) (Pub. L. 107-273, 116 Stat. 1758 (2002)), which further amended 35 U.S.C. § 102(e), as revised by the American Inventors Protection Act of 1999 (AIPA) (Pub. L. 106-113, 113 Stat. 1501 (1999)). The revised provisions in 35 U.S.C. § 102(e) are completely retroactive and effective immediately for all applications being examined or patents being reexamined. Until all of the Office's automated systems are updated to reflect the revised statute, citation to the revised statute in Office actions is provided by this attachment. This attachment also substitutes for any citation of the text of 35 U.S.C. § 102(e), if made, in the attached Office action.

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102 in view of the AIPA and H.R. 2215 that forms the basis for the rejections under this section made in the attached Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another

filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102 prior to the amendment by the AIPA that forms the basis for the rejections under this section made in the attached Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

For more information on revised 35 U.S.C. § 102(e) visit the USPTO website at www.uspto.gov or call the Office of Patent Legal Administration at (703) 305-1622.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

5 DSR
JANUARY 12, 2003